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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,592	07/20/2001	Jonathan M. Friedman	389004/039 JJD/BO	1403

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James F. Haley, Jr., Esq
c/o FISH & NEAVE
1251 AVENUE OF THE AMERICAS
50TH FLOOR
NEW YORK, NY 10020

EXAMINER

LY, CHEYNE D

ART UNIT

PAPER NUMBER

1631

10

DATE MAILED: 06/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/910,592

Applicant(s)

FRIEDMAN, JONATHAN M.

Examiner

Cheyne D Ly

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23,37,39-53 and 61-69 is/are pending in the application.
- 4a) Of the above claim(s) 13 and 63-69 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-12,14-23,37 and 39-53 is/are rejected.
- 7) ☒ Claim(s) 10, 11, and 16 is/are objected to.
- 8) ☒ Claim(s) 1-23,37,39-53 and 61-69 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on April 16, 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Applicant's election of Group I, claims 1-23, 36, 39-53, and 61-69; species macromolecular compound and structure has been determined for a molecule of interest without further ligand or drug binding or interaction consideration, Paper No. 9, filed April 16, 2003, is acknowledged. Because applicant did not distinctly and specifically traverse the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 13 and 63-69 have been withdrawn due to being not directed to the elected species.

1. Claims 1-12, 14-23, 37, 39-53, 61, and 62 are examined on the merits.

OBJECTIONS

2. The title of the invention is not descriptive the claimed invention is a method for determining the three-dimensional structure of a molecule of interest and the current title does not fully describe the claimed invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

3. Claim 10, line 2, is objected to because of the following informalities: The term "of" is not properly used. Appropriate correction is required.

4. Claim 11, line 2, is objected to because of the following informalities: The term "initialing" is misspelled. Appropriate correction is required.

5. Claim 16 is objected to due to the inclusion of subject matter, which has been non-elected due to a restriction requirement and therefore withdrawn from consideration.

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6. The disclosure is objected to because of the following informalities: The instant specification contains incomplete references to citations or figures (Page 9, line 8 and 9).

Appropriate correction is required.

CLAIM REJECTIONS - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61, and 62 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.

9. It is acknowledged that the claim subject matter is a method for determining the three-dimensional structure of a molecule of interest. However, claims 1-12, 14, 16-23, 37, 39-53, 61, and 62 are rejected because they are directed to a non-statutory subject matter due to lacking any physical steps such as displaying the molecule of interest. Currently, the steps are merely algorithmic processes of manipulating data directed to a molecule of interest without providing a means of visualizing the results of the said processes; therefore, the claim subject matter lacks a real world value. The critical steps of displaying the molecule interest would cause the subject matter in its entirety to be a statutory application.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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11. Claims 1-12, 14-23, 37, 39-53, 61, and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Specific to claims 1 and 48, step (f), line 3, the term “becomes” causes the claim to be vague and indefinite because it is unclear how each spherical harmonic spherical Bessel basis function becomes a Fourier representation. Does each spherical harmonic spherical Bessel basis function spontaneously become a Fourier representation, or due to some data analysis or data manipulation? Step (g) of claims 1 and 48 further causes the claim to be vague and indefinite because it is unclear how the calculation of the Fourier representation of each spherical harmonic spherical Bessel basis function is accomplished in step (g) when such step has been achieved in step (f). Clarification of the metes and bounds is required. Claims 2-12, 14-23, 37, 39-47, 49-53, 61, and 62 are rejected for being dependent from claim 1 or 48.

13. Specific to claims 1, steps (h) and (i), line 1; 39, line 3; 40, line 2; and 48, step (h), line 1, the term “complex-valued” causes the claims to be vague and indefinite because it is unclear what criteria is being used to consider that a coefficient is “complex-valued” (crystal structure of a complex comprising a receptor and a ligand or the difficulty of determining the coefficients). Clarification of the metes and bounds is required. Claims 2-12, 14-23, 37, 39-47, 49-53, 61, and 62 are rejected for being dependent from claim 1 or 48.

14. Claims 1 and 48, step (h), line 4, recites the limitation "experimental x-ray diffraction data." There is insufficient antecedent basis for this limitation in the claim. Claims 2-12, 14-23, 37, 39-47, 49-53, 61, and 62 are rejected for being dependent from claim 1 or 48.

15.

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16. Claim 2, line 2, recites the limitation "diffracting molecule." There is insufficient antecedent basis for this limitation in the claim.

17. Specific to claims 2, line 5; and 9, line 3, the term "improvements" causes the claim to be vague and indefinite because it is unclear what is being improved (the process of modeling or the data generated from the process). Clarification of the metes and bounds are required.

18. Specific to claim 48, step (b), line 1, the phrase "more often" causes the claim to be vague and indefinite because it is unclear what is being used to consider "more often." Is choosing more than one time "more often"? Clarification of the metes and bounds of the instant claims is required. Claims 49-53, 61, and 62 are rejected for being dependent from claim 48.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61, and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease, does not reasonably provide enablement for any other molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

21. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The

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factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

22. It is acknowledged that the applicant has disclosed information to enable one skilled in the art to use the said method specific specifically for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease (Page 33, lines 21-25). However, a method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said method. It is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized.

Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002). Accordingly, it would be unpredictable for one skilled in the art to use the said method to determine the three-dimensional structure of any other molecule beyond the ones of the instant case. In light of the difficulty of the protein

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crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the information disclosed for one specific crystal to use the claimed invention on any other of predictable quality without undue experimentation.

23. Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61, and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease using equations 1-12 (pages 10-14), does not reasonably provide enablement for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease using any other mathematical equation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

24. It is acknowledged that the applicant has disclosed information to enable one skilled in the art to use the said method specific specifically for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease (Page 33, lines 21-25 and equations 1-12, pages 10-14). It would be unpredictable for one skilled in the art to use the said method to determine the three-dimensional structure using any other mathematical equation beyond the ones of the instant case. In light of the difficulty of the protein crystallization process as discussed above and the lack of guidance of using any other mathematical equations, it is, therefore, unreasonable to expect one skilled in the art to use the information disclosed for one specific crystal to use the claimed invention on any other of predictable quality without undue experimentation.

CLAIM REJECTIONS - 35 USC § 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

26. Claims 1-12, 14-23, 37, 39-53, 61, and 62 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Friedman (January 1999).

27. Friedman (1999) discloses a method for interconverting three-dimensional molecular spatial information with spherical harmonic-Bessel representation and non-centrosymmetric crystalline arrays (Abstract etc.), as in claims 37 and 49.

28. The method of Friedman has been tested with a few macromolecular crystals of known structure (page 22, column 2, lines 44-45), as in claims 1, 48, step (a); 3; 16; and 50.

29. Exhaustive searches are performed to find the position and rotational orientation of a known molecule in a new crystalline packing arrangement based upon a measured X-ray diffraction pattern and the Fourier phase information associated with the diffraction pattern is initially unknown (page 10, column 1, lines 21-30), as in claims 4 and 51. The inclusion of a reference by Berikov et al. is not used as prior art but only as a reference to expand on the step of exhaustive searches. Berikov et al. disclose an exhaustive search method involving decision tree construction with a recursive algorithm (page 555, column 2, lines 1-11 and Figure 4).

30. The said method based upon orthogonal basis functions allows for two of the final three rotational degrees of freedom to be handled by FFT and for the final rotation to be calculated rapidly by multiplying spherical harmonic coefficients by a matrix. Friedman discloses the use

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software such as DOCK for modeling the docking of ligands into protein (page 11, column 2, lines 2-56), as in claims 1, 48, step (b); and claim 2, step (k).

31. A resolution limit of 3.0 Å is used in the evaluation of the FFTs (page 14, column 2, lines 2-3), as in claims 1 and 48, step (c).

32. Two arbitrary geometric parameters, radius and position, are determined for the unit cell lengths and angles in terms of the Fourier expansion (page 12, column 1, lines 1-34), as in claims 1 and 48, steps (d) and (g); and claim 6.

33. The prescreen step reduces the number of translation points that need to be considered (page 13, column 2, lines 52-54), as in claims 1 and 48, step (e).

34. The interconversion between the spherical harmonic-Bessel representation and the Fourier representation can be calculated (page 10, column 1, lines 10-13), as in claims 1 and 48, step (f). Further, the value of zero is considered in the said calculations (page 16, equations 6-8), as in claim 10.

35. Complex-valued coefficients, Fourier summations, indices are calculated according to equations 3-5 (pages 15 and 16), as in claims 1, 48, steps (h), (i), and (j); 7; 8; 9; 11; and 39-42.

36. The said method is designed to provide functional maxima or minima for each of the energy terms (page 21, column 2, lines 16-17), as in claim 2, step (l).

37. One may use the said method for non-overlapping spherical expansion zones (page 21, column 2, lines 38-45), as in claim 5.

38. Equations 6-8 are used for converting from a series of spherical harmonic coefficients to one of Fourier structure factor amplitudes and phases (page 16, lines 26-28), as in claim 12.

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39. DEC-alpha-4000 workstation is being used data input and output (page 14, column 2, lines 11-17) and model being displayed (Figures 1 and 2), as in claims 14, 15, 17-23, 43-47, 52, 53, 61, and 62.

CONCLUSION

40. NO CLAIM IS ALLOWED.

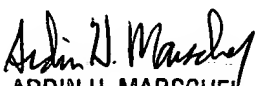
41. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

42. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

43. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

44. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
6/10/03


ARDIN H. MARSCHEL
PRIMARY EXAMINER